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EVALUATION OF THE EFFECTIVENESS OF GRISEOFULVIN, TOLNAFTATE, AND PLACEBO IN THE TOPICAL THERAPY OF SUPERFICIAL DERMATOPHYTOSES

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The efficacy of a topical formulation containing 2% micronized griseofulvin applied 3 times daily for 3 weeks was evaluated in patients with superficial dermatophytoses. A double-blind parallel study was designed to compare the formulation to a standard therapy (tolnaftate 1% cream) and a placebo ointment. One of the 3 preparations was assigned at random to a total of 52 subjects. Thirteen of 15 subjects treated with placebo ointment were judged to be treatment failures. Nine of 18 subjects treated with griseofulvin, and 9 of 19 subjects treated with tolnaftate, responded to treatment. Clinical response appeared to be related to the severity of the infection rather than to the anatomical location of the lesions. The results suggest that griseofulvin may be effective following topical application and demonstrate the usefulness of positive and negative controls when evaluating topical antifungal agents.

It is commonly believed that griseofulvin is ineffective when used topically. The origin of this notion is difficult to identify since early reports of the efficacy [1] or the failure [2] of various formulations containing the compound were merely passing references to unpublished trials. Results from one study that suggested efficacy in the treatment of tinea pedis [3] are difficult to interpret. Three different griseofulvin formulations were tested against placebo, but the allocation of the treatments did not appear to have been randomized and there was no indication that the trial was conducted double blind. More recently, an ointment formulation has been reported to be effective [4] and two reviews suggest that topical administration of griseofulvin may be a useful method of therapy [5,6]. However, references to clinical studies to support this conclusion were not provided. As Goldman stated [7], this route of administration remains in the area of experimental therapeutics.

Therapeutic efficacy of a topical formulation of any drug depends upon the availability of the compound for absorption and its subsequent penetration in sufficient concentrations to the site of action. As well, therapeutic activity must be assessed in properly designed clinical trials utilizing appropriate disease entites and treatment must be of adequate frequency and duration. Early animal investigations revealed that topically applied griseofulvin was effective in treating experimental fungal infections [8], but the ambiguous results during trials in humans may have been responsible for focusing attention on the local factors which influence response. For example, availability of griseofulvin and subsequent skin penetration may not be the limiting factors to efficacy. With the development of suitably sensitive techniques for measuring small amounts of griseofulvin in human skin [9], it was possible to demonstrate that a single application of an ointment containing 2% micronized griseofulvin to healthy skin produced skin concentrations of the drug several times higher than those measured after oral administration (Riegelman S, Epstein W: personal communication). The following study was designed to evaluate the efficacy of this formulation in the treatment of superficial fungal infections of human skin. The efficacy of the prepartation was compared under double-blind conditions with that of a placebo ointment and 1% tolnaftate cream. The results with the test preparation were evaluated with respect to those with the positive control (tolnaftate) and the negative control (placebo).

MATERIALS AND METHODS

Subjects were selected from adults attending Duke University Medical Center outpatient dermatology clinics. The purpose of the investigation and the double-blind controlled nature of the trial were explained to each subject and informed consent was obtained. Patients with the following were excluded from the investigation: dermatophytosis involving the hair and scalp and/or nails; lesions with secondary bacterial infections; those who had used griseofulvin or tolnaftate preparations within three months of admission to the study.

During the initial clinic visit the diagnosis of a new or recurrent superficial dermatophytosis was confirmed by microscopic examination of skin scrapings dissolved in

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10% potassium hydroxide. Sabouraud's agar plates were inoculated with material from the lesions. Subjects were assigned an investigational number in the order of their admission to the trial and were treated for 3 weeks with one of the topical preparations. They were examined weekly for response to treatment. One week after completion of the treatment regime, the subjects were requested to return for a follow-up visit in order to repeat the KOH examination and culture of material from any remaining lesions or to determine whether a recurrence had occurred following apparently successful therapy. On the initial visit and at the completion of therapy, hemoglobin concentration, white blood cell count, urinalysis, concentrations of serum bilirubin, SGOT, and alkaline phosphatase were obtained.

Patients received one of the three following medications according to a predetermined randomized treatment schedule: micronized griseofulvin, 2% concentration in an ointment base; ointment base only; tolnaftate, 1.0% concentration in a cream base (Supplied as Tinactin, Schering Corporation). Preinvestigation comparisons of the three preparations showed that they were nearly identical in appearance, but that the ointment preparations were slightly more greasy in consistency than the tolnaftate cream. Patients were instructed to apply the medication to the infected areas daily for 3 weeks; twice during the daytime and at bedtime after bathing the infected areas. Investigational material for each subject was supplied in three 15-gm tubes and one tube of medication was dispensed at each visit. All labels identifying the contents had been removed and replaced by a plain label containing the patient's study number.

Response to treatment was judged by the clinical response after 3 weeks of therapy and the results of the follow-up KOH exam and culture. In order to be considered a treatment success, a lesion must have cleared completely during the 3 treatment weeks, or have improved markedly and be accompanied by a negative follow-up KOH exam and culture. Any other response, including recurrence at the follow-up visit, was considered to be a treatment failure.

Before breaking the double-blind code at the end of the trial the clinical course of each individual patient was reviewed. It became apparent that the severity of the infections was variable from subject to subject. Therefore, patients were classified as having "severe" infections at the time of admission to the study if their infections satisfied at least one of the following three description: (1) lesions covered by a thick horny scale that were persistent and/or chronic; (2) lesions with a marked local inflammatory response suggesting a localized hypersensitivity reaction to the infecting microorganism; and (3) lesions involving large surface areas of the body. The remainder of the patients whose lesions did not conform to these clinical descriptions were classified as "not severe."

Standard chi square techniques were utilized to evaluate homogeneity of the treatment groups and for comparison of the results. A Fisher Exact Probability Test for 2 $\times$ 2 contingency tables was used when small expected values were encountered. The results were considered to be due to chance if p was found to be greater than 0.05.

RESULTS

Fifty-seven patients, predominantly white males (only 8 were female and 4 non-white), ranging in age from 20 to 64 years, were admitted to the study. One patient was excluded because of a combined yeast-fungal infection, 1 was lost from the investigation because of admission to the hospital for elective surgery, and 3 moved away. Of the 5 subjects lost, 3 had received placebo, 1 griseofulvin, and 1 tolnaftate. Three subjects were withdrawn from the investigation before the 3-week period of treatment was concluded because of marked worsening of their infections and were considered to be treatment failures. Two of these were on placebo and the other tolnaftate. Two subjects who were treatment successes did not return for a follow-up visit 1 week after discontinuing treatment. One had received griseofulvin and the other tolnaftate and both are included in the analysis of the results. All subjects except 2 required one tube of medication per week in order to treat their infection, and therefore the dose applied can be assumed to have been fairly uniform for the majority of the subjects. In no instances were adverse reactions to therapy encountered.

Therefore, data from 52 patients was available for analysis. The clinical diagnosis was tinea pedis in 31 instances, tinea cruris in 10, tinea corporis in 3, and tinea manuum in 2. In the remaining 6 cases, the clinical diagnosis was that of a combined infection consisting of two of the above anatomical sites excluding feet. A higher proportion of griseofulvin-treated patients had tinea pedis infections (Tab. I), but the difference was not statistically significant.

Twenty-four subjects were classified as having infection of a "severe" nature. The remaining 28 had infections classified as "not severe." There was no difference in the distribution of severe cases among the treatment regimes (Tab. I).

Potassium hydroxide preparations of skin scrapings from the lesions were positive when examined by microscope for branching hyphae in all 52 cases on the admission visit. The initial cultures taken at this time were positive in 33 cases, yielded no growth in 13 cases, and were contaminated with overgrowth in 6 cases. The infecting microorganisms were *Trichophyton mentagrophytes* (14 cases), *Trichophyton rubrum* (12 cases), *Epidermophyton floccosum* (6 cases), and *Trichophyton tonsurans* (1 case). A mycologic diagnosis was made with greater frequency in subjects receiving tolnaftate (Tab. I). However, this difference was not significant at $p < 0.05$.

Upon completion of the investigation, decoding revealed that 18 subjects had received griseofulvin, 19 tolnaftate, and 15 placebo (Tab. II). Of the 21 subjects classified as experiencing a beneficial response, 19 were given one of the two active preparations (9 received griseofulvin, 10 received tolnaftate). Only 2 subjects with a successful response received placebo. While each of the two active treatments proved to be significantly superior to placebo, no difference was observed between griseofulvin and tolnaftate.

Twenty-four subjects were considered to have "severe" infections. Seven of these received griseo-

TABLE I. *The distribution of 52 patients with superficial dermatophytoses with respect to treatment regime, anatomical site of infection, severity of infection, and mycologic diagnosis*

		Treatment			Chi square
		Griseofulvin 2% ointment (18 patients)	Tolnaftate 1.0% cream (19 patients)	Placebo ointment base (15 patients)	
Anatomical site	Tinea pedis	13	10	8	N.S.[a]
	All other sites	5	9	7	
Classification of severity of the infection	Severe	7	10	7	N.S.[a]
	Not severe	11	9	8	
Mycological diagnosis	Admission culture positive	9	16	8	$0.10 > p > 0.05$
	Admission culture not diagnostic	9	3	7	

[a] N.S. = not significant.

TABLE II. *The clinical-laboratory evaluation of the response to treatment in 52 patients with superficial dermatophytoses treated for 21 days with topical application of griseofulvin, tolnaftate, or placebo*

Response	Treatment[a]		
	Griseofulvin 2% ointment	Tolnaftate 1.0% cream	Placebo ointment base
Treatment success	9	10	2
Treatment failures	9	9	13
Totals	18	19[b]	15

[a] Chi square for difference between the 3 treatments = $p < 0.05$.

[b] Fisher exact probability test for griseofulvin versus tolnaftate: not significant.

TABLE III. *The clinical-laboratory evaluation of the response to treatment in 52 patients classified as having severe and not severe superficial dermatophytoses infections*

Response	Treatment of 24 patients with severe infections[a]			Treatment of 28 patients with not severe infections[b]		
	Griseofulvin 2% ointment	Tolnaftate 1.0% cream	Placebo ointment base	Griseofulvin 2% ointment	Tolnaftate 1.0% cream	Placebo ointment base
Treatment success	1	3	1	8	7	1
Treatment failures	6	7	6	3	2	7
Totals	7	10	7	11	9	8

[a] Fisher exact probability test for griseofulvin versus tolnaftate: not significant.

[b] Fisher exact probability test for griseofulvin versus tolnaftate: not significant.

fulvin, 10 tolnaftate, and 7 placebo (Tab. III). While the number of subjects in each case is small, there would appear to be no differences between the treatments since the majority of "severe" cases treated resulted in a failure of therapy. For the 28 subjects with a "not severe" infection, no difference was observed between the effectiveness of either griseofulvin or tolnaftate, and placebo was ineffective. Therefore, both active agents were effective in "not severe" cases but not very different from placebo in "severe" cases.

More than half of the patients treated had "athletes foot" (Tab. IV). Infections in this site were not more resistant to treatment than infections of other anatomical sites.

Admission cultures were not diagnostic in 19 subjects, usually because of failure of the dermatophyte to grown. The preponderance of mycologic diagnosis noted in the tolnaftate treatment group (Tab. I) is reflected in Table V as a higher proportion of patients treated successfully with tolnaftate. However, the total number of cases treated successfully with either griseofulvin or tolnaftate is similar.

No relationship between medication and speed of response was apparent. When improvement occurred, it was evident within 1 week of instituting therapy.

A recurrence at the time of the follow-up visit occurred in only 1 patient in the trial. This subject received griseofulvin and was considered a treatment failure.

TABLE IV. *The response to treatment in 52 patients with superficial dematophytoses with respect to anatomical site of infection*

	Griseofulvin 2.0% ointment		Tolnaftate 1.0% cream		Placebo ointment base		Totals[a]	
	Success	Failure	Success	Failure	Success	Failure	Success	Failure
Tinea pedis (13 patients)	7	6	5	5	1	7	13	18
All others (21 patients) (tinea cruris, corporis, manuum, and combined infections)	2	3	5	4	1	6	8	13
Totals	9	9	10	9	2	13	21	31

[a] Chi square test on the total number of successes and failures in relation to the site of infection: not significant.

TABLE V. *The response to treatment in 52 patients with superficial dematophytoses with respect to mycologic diagnosis*

	Treatment							
	Griseofulvin 2% ointment		Tolnaftate 1% cream		Placebo ointment base		Totals[a]	
	Success	Failure	Success	Failure	Success	Failure	Success	Failure
Admission culture positive	3	6	9	7	0	8	12	21
Admission culture not diagnostic	6	3	1	2	2	5	9	10
Totals	9	9	10	9	2	13	21	31

[a] Chi square test of the total number of successes and failures in relation to the result of the admission culture: not significant.

DISCUSSION

Random distribution of the patients to the three treatments resulted in groups that were similar with respect to sex and race and such local factors as severity of the infection and anatomical site of the infection. Both griseofulvin and tolnaftate were similar in effect and superior to placebo, independent of the site of infection.

The criteria for stratifying patients as having "severe" infection were based upon the consideration that these cases, with justification, could have been treated systemically for a short period of time in conjunction with local therapy. Although the classification may be criticized because it was undertaken after the investigation was completed rather than used for pretrial stratification, its usefulness for interpretation of the results is valid because it was carried out prior to decoding the treatments. The resistance of "severe" cases to the two active preparations (76% failure) suggests that failure was related to the severity of the lesion. The percentage of successes in the "not severe" group (75%) approaches that reported from investigations with other topical agents [10–13]. Therefore, under the conditions used in this study, the availability and subsequent penetration of griseofulvin and tolnaftate were adequate for treating some infections.

The number of instances in which a pretreatment mycologic diagnosis was made, while not statistically different, favored the tolnaftate treatment. It is not uncommon to experience difficulty in obtaining cultures from "ring worm" infections either because of failure of an organism to grow or due to a rapid overgrowth of contaminants. Since all patients had positive KOH preparations, it is unlikely that patients with nonspecific infections were included in the investigation.

The results of this study indicate the value of including negative as well as positive controls when evaluating topical antifungal agents. The frequency of success of both active preparations is much more meaningful when compared to the ineffectiveness of placebo treatment, particularly when relatively small numbers of cases are studied. In addition, the results suggest that trialists should consider prestratifying cases according to the severity of the infection as well as other factors that are generally assumed to modify response.

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